L Number	Hits	Search Text	DB	Time stamp
-	30	besterman-$.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/05/02 16:39
-	2	besterman-$.in. and (methyltransferase or (methyl adj transferase))	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/05/02 16:15
-	1	2001-016407.NRAN.	DERWENT	2002/05/02 16:17
-	1	2000-339532.NRAN.	DERWENT	2002/05/02 16:38
-	3241	combination adj therapy	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/05/02 16:40
-	180	(combination adj therapy) and (gene adj therapy)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/05/02 16:40
-	102	((combination adj therapy) and (gene adj therapy)) and antisense	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/05/02 16:41
-	0	(((combination adj therapy) and (gene adj therapy)) and antisense) and ((aza or fluoro or dihydro) adj (cytidine or deoxycytidine or cytosine or deoxycytosine))	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/05/02 16:43
-	60	antisense and ((aza or fluoro or dihydro) adj (cytidine or deoxycytidine or cytosine or deoxycytosine))	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/05/02 16:43
-	36	(antisense and ((aza or fluoro or dihydro) adj (cytidine or deoxycytidine or cytosine or deoxycytosine))) and tumor	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/05/02 16:43
-	5	((antisense and ((aza or fluoro or dihydro) adj (cytidine or deoxycytidine or cytosine or deoxycytosine))) and tumor) and (synergistic or synergism)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/05/02 16:48
-	199	dna adj (methyltransferase or (methyl adj transferase))	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/05/02 16:49
-	3	(antisense and ((aza or fluoro or dihydro) adj (cytidine or deoxycytidine or cytosine or deoxycytosine))) and (dna adj (methyltransferase or (methyl adj transferase)))	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/05/02 16:49

(FILE 'HOME' ENTERED AT 17:02:01 ON 02 MAY 2002)

FILE 'CAPLUS, MEDLINE, BIOSIS' ENTERED AT 17:02:58 ON 02 MAY 2002

L1 2021 FILE CAPLUS
L2 2730 FILE MEDLINE
L3 1966 FILE BIOSIS
TOTAL FOR ALL FILES
L4 6717 S DNA (W) METHYLTRANSFERASE
L5 69 FILE CAPLUS
L6 44 FILE MEDLINE
L7 43 FILE BIOSIS
TOTAL FOR ALL FILES
L8 156 S L4 AND ANTISENSE
L9 23 FILE CAPLUS
L10 15 FILE MEDLINE
L11 9 FILE BIOSIS
TOTAL FOR ALL FILES
L12 47 S L8 AND INHIBITOR
L13 1 FILE CAPLUS
L14 0 FILE MEDLINE
L15 0 FILE BIOSIS
TOTAL FOR ALL FILES
L16 1 S L12 AND (DEOXYCYTOSINE OR DEOXYCYTIDINE)
L17 6 FILE CAPLUS
L18 6 FILE MEDLINE
L19 1 FILE BIOSIS
TOTAL FOR ALL FILES
L20 13 S L12 AND (CYTOSINE OR CYTIDINE)
L21 11 DUP REM L20 (2 DUPLICATES REMOVED)
E 5'-AZA-2'-DEOXY
L22 0 FILE CAPLUS
L23 0 FILE MEDLINE
L24 0 FILE BIOSIS
TOTAL FOR ALL FILES
L25 0 S "5'-AZA-2'-DEOXYCYTOSINE"
L26 0 FILE CAPLUS
L27 0 FILE MEDLINE
L28 0 FILE BIOSIS
TOTAL FOR ALL FILES
L29 0 S "5'-AZA-DEOXYCYTOSINE"
L30 0 FILE CAPLUS
L31 0 FILE MEDLINE
L32 0 FILE BIOSIS
TOTAL FOR ALL FILES
L33 0 S AZA(W)DEOXYCYTOSINE
L34 17 FILE CAPLUS
L35 22 FILE MEDLINE
L36 28 FILE BIOSIS
TOTAL FOR ALL FILES
L37 67 S AZA(W)DEOXYCYTIDINE
L38 0 FILE CAPLUS
L39 2 FILE MEDLINE
L40 0 FILE BIOSIS
TOTAL FOR ALL FILES
L41 2 S FLUORO(W)DEOXYCYTIDINE
L42 0 FILE CAPLUS
L43 0 FILE MEDLINE
L44 0 FILE BIOSIS
TOTAL FOR ALL FILES
L45 0 S L39 AND L37

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L46          17 FILE CAPLUS
L47          24 FILE MEDLINE
L48          28 FILE BIOSIS
     TOTAL FOR ALL FILES
L49          69 S L39 OR L37
L50           0 FILE CAPLUS
L51           0 FILE MEDLINE
L52           0 FILE BIOSIS
     TOTAL FOR ALL FILES
L53           0 S L49 AND (METHYL(W)TRANSFERASE)
L54           4 FILE CAPLUS
L55           7 FILE MEDLINE
L56           7 FILE BIOSIS
     TOTAL FOR ALL FILES
L57          18 S L49 AND (METHYLTRANSFERASE)
L58          10 DUP REM L57 (8 DUPLICATES REMOVED)
L59           4 S L58
L60           0 FILE CAPLUS
L61           5 S L58
L62           0 FILE MEDLINE
L63           1 S L58
L64           0 FILE BIOSIS
     TOTAL FOR ALL FILES
L65           0 S L58 AND ANTISENSE
L66           4 S L58
L67           0 FILE CAPLUS
L68           5 S L58
L69           0 FILE MEDLINE
L70           1 S L58
L71           0 FILE BIOSIS
     TOTAL FOR ALL FILES
L72           0 S L58 AND (RIBOZYME OR APTAMER OR TRIPLEX OR ANTISENSE OR (ANTI
L73          18 FILE CAPLUS
L74           2 FILE MEDLINE
L75           6 FILE BIOSIS
     TOTAL FOR ALL FILES
L76          26 S (METHYL(W)TRANSFERASE) AND (RIBOZYME OR APTAMER OR TRIPLEX OR
L77          17 FILE CAPLUS
L78           2 FILE MEDLINE
L79           5 FILE BIOSIS
     TOTAL FOR ALL FILES
L80          24 S (METHYL(W)TRANSFERASE) AND (ANTISENSE OR (ANTI(W)SENSE))
L81          22 DUP REM L80 (2 DUPLICATES REMOVED)
L82          22 FOCUS L81 1-
L83        3070 FILE CAPLUS
L84         861 FILE MEDLINE
L85        1477 FILE BIOSIS
     TOTAL FOR ALL FILES
L86        5408 S JU ?/AU
L87           0 FILE CAPLUS
L88           0 FILE MEDLINE
L89           0 FILE BIOSIS
     TOTAL FOR ALL FILES
L90           0 S L86 AND (METHYL(W)TRANSFERASE)
L91           0 FILE CAPLUS
L92           0 FILE MEDLINE
L93           1 FILE BIOSIS
     TOTAL FOR ALL FILES
L94           1 S L86 AND (METHYLTRANSFERASE)
L95        2149 FILE CAPLUS
L96        2371 FILE MEDLINE
L97        3328 FILE BIOSIS
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     TOTAL FOR ALL FILES
L98         7848 S DRUG (W) SENSITIVITY
L99            1 FILE CAPLUS
L100           0 FILE MEDLINE
L101           0 FILE BIOSIS
     TOTAL FOR ALL FILES
L102           1 S L98 AND L86

     FILE 'STNGUIDE' ENTERED AT 17:31:31 ON 02 MAY 2002

=>
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L58 ANSWER 1 OF 10 MEDLINE
ACCESSION NUMBER: 2002211750 IN-PROCESS
DOCUMENT NUMBER: 21942399 PubMed ID: 11948118
TITLE: Silencing of GSTP1 Gene by CpG Island DNA Hypermethylation in HBV-associated Hepatocellular Carcinomas.
AUTHOR: Zhong Sheng; Tang Mandy W; Yeo Winnie; Liu Cuiling; Lo Y M Dennis; Johnson Philip J
CORPORATE SOURCE: Departments of Clinical Oncology [S. Z., M. W. T., W. Y., C. L., P. J. J.] and Chemical Pathology [Y. M. D. L.], Sir Y. K. Pao Centre for Cancer, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, N. T., Hong Kong SAR, China.
SOURCE: CLINICAL CANCER RESEARCH, (2002 Apr) 8 (4) 1087-92. Journal code: 9502500. ISSN: 1078-0432.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20020412
Last Updated on STN: 20020412

AB Purpose and Experimental Design: Glutathione S-transferases, enzymes that defend cells against damage mediated by oxidant and electrophilic carcinogens, may be critical determinants of cancer pathogenesis. In this report, we assess the role of epigenetic silencing of the GSTP1 gene, a gene encoding the pi-class glutathione S-transferase, in the pathogenesis of hepatitis B virus (HBV)-associated hepatocellular carcinomas (HCC). The cell lines Hep3B, HepG2, and a cohort of 43 HBV-associated HCC tissue specimens and corresponding nontumor tissues were subjected to analysis for GSTP1 epigenetic alteration and expression. GSTP1 "CpG" island DNA hypermethylation in the liver cell lines, and the tissue specimens were determined by methylation-specific PCR and correlated with expression of the gene using reverse-transcription PCR, immunoblotting, and immunohistochemistry. RESULTS: GSTP1 CpG island DNA hypermethylation was detected in 28 of 43 (65.1%) HCC tissues and 4 of 40 (10%) corresponding nontumor tissues. GSTP1 protein was absent in those cases showing hypermethylation of the gene. Similarly, DNA from Hep3B and HepG2 cell lines displayed complete GSTP1 hypermethylation in the CpG island, and they failed to express GSTP1 mRNA and the corresponding protein product. Treatment of the cell lines with the DNA **methyltransferase** inhibitor 5-**aza-deoxycytidine** reversed the hypermethylation, and restored GSTP1 mRNA and polypeptide expression. CONCLUSIONS: These data indicate that epigenetic silencing of GSTP1 gene expression by CpG island DNA hypermethylation is common in human HBV-associated HCC. In addition, somatic GSTP1 inactivation via CpG island hypermethylation may contribute to the pathogenesis of this malignancy.

L58 ANSWER 2 OF 10 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 1
ACCESSION NUMBER: 2002:12723 CAPLUS
TITLE: Reversal of GSTP1 CpG island hypermethylation and reactivation of .pi.-class glutathione S-transferase (GSTP1) expression in human prostate cancer cells by treatment with procainamide
AUTHOR(S): Lin, Xiaohui; Asgari, Kekule; Putzi, Mathew J.; Gage, Wesley R.; Yu, Xiang; Cornblatt, Brian S.; Kumar, Arunima; Piantadosi, Steven; DeWeese, Theodore L.; De Marzo, Angelo M.; Nelson, William G.
CORPORATE SOURCE: Department of Oncology, The Johns Hopkins University School of Medicine, Baltimore, MD, 21231, USA
SOURCE: Cancer Research (2001), 61(24), 8611-8616 CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal
LANGUAGE: English
AB Among the many somatic genome alterations present in cancer cells, changes in DNA methylation may represent reversible "epigenetic" lesions, rather than irreversible "genetic" alterations. Cancer cell DNA is typically characterized by increases in the methylation of CpG dinucleotides clustered into CpG islands, near the transcriptional regulatory regions of crit. genes, and by an overall redn. in CpG dinucleotide methylation. The transcriptional "silencing" of gene expression assocd. with such CpG island DNA hypermethylation presents an attractive therapeutic target: restoration of "silenced" gene expression may be possible via therapeutic reversal of CpG island hypermethylation. 5-Aza-cytidine (5-aza-C) and 5-**aza-deoxycytidine** (5-aza-dC), nucleoside analog inhibitors of DNA **methyltransferases**, have been widely used in attempts to reverse abnormal DNA hypermethylation in cancer cells and restore "silenced" gene expression. However, clin. utility of the nucleoside analog DNA **methyltransferase** inhibitors has been limited somewhat by myelosuppression and other side effects. Many of these side effects are characteristic of nucleoside analogs that are not DNA **methyltransferase** inhibitors, offering the possibility that nonnucleoside analog DNA **methyltransferase** inhibitors might not possess such side effects. Human prostate cancer (PCA) cells characteristically contain hypermethylated CpG island sequences encompassing the transcriptional regulatory region of GSTP1, the gene encoding the .pi.-class glutathione S-transferase (GSTP1), and fail to express GSTP1 as a consequence of transcriptional "silencing.". Inactivation of GSTP1 by CpG island hypermethylation, the most common somatic genome alteration yet reported for human PCAs, occurs early during human prostatic carcinogenesis and results in a loss of GSTP1 "caretaker" function, leaving prostate cells with inadequate defenses against oxidant and electrophile carcinogens. We report here that the drug procainamide, a nonnucleoside inhibitor of DNA **methyltransferases**, reversed GSTP1 CpG island hypermethylation and restored GSTP1 expression in LNCaP human PCA cells propagated in vitro or in vivo as xenograft tumors in athymic nude mice.
REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L58 ANSWER 3 OF 10 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:795150 CAPLUS
DOCUMENT NUMBER: 136:144777
TITLE: 5-Aza-2'-deoxycytidine Induces Histone Hyperacetylation of Mouse Centromeric Heterochromatin by a Mechanism Independent of DNA Demethylation
AUTHOR(S): Takebayashi, Shin-ichiro; Nakao, Mitsuyoshi; Fujita, Naoyuki; Sado, Takashi; Tanaka, Minoru; Taguchi, Hiroshi; Okumura, Katsuzumi
CORPORATE SOURCE: Faculty of Bioresources, Mie University, Tsu, Mie, 514-8507, Japan
SOURCE: Biochemical and Biophysical Research Communications (2001), 288(4), 921-926
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB 5-Aza-2'-deoxycytidine (5-azadC) is widely used as a potent inhibitor of DNA **methyltransferase**. Cells treated with this drug show various phenomena such as the reactivation of repressed genes, change in replication timing, and decondensation of heterochromatin. A no. of studies using this drug have been reported so far but it is still controversial whether such changes are due to 5-azadC-induced demethylation itself or the side effects of the drug. Here we report that

5-azadC treatment induces histone hyperacetylation in mouse centromeric heterochromatin which normally contains methylated DNA and hypoacetylated histones. Treatment also affects the intranuclear distribution of histone deacetylase 2 (HDAC2). However, histone hyperacetylation was not obsd. in DNA **methyltransferase** 1-deficient cells with a reduced level of genomic DNA methylation. Our results suggest that 5-azadC-induced histone hyperacetylation is independent of DNA demethylation and that DNA methylation is not essential for the maintenance of the histone hypoacetylated state in centromeric heterochromatin. (c) 2001 Academic Press.

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L58 ANSWER 4 OF 10 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:209957 BIOSIS
DOCUMENT NUMBER: PREV200200209957
TITLE: Minimal effective dose of the hypomethylating agent Decitabine in hematopoietic malignancies.
AUTHOR(S): Issa, Jean-Pierre (1); Garcia-Manero, Guillermo (1); Mannari, Rajan (1); Thomas, Deborah (1); Giles, Frank (1); Cortes, Jorge (1); Estey, Elihu (1); Kantarjian, Hagop (1)
CORPORATE SOURCE: (1) Department of Leukemia, University of Texas M.D. Anderson Cancer Center, Houston, TX USA
SOURCE: Blood, (November 16, 2001) Vol. 98, No. 11 Part 1, pp. 594a-595a. http://www.bloodjournal.org/. print.
Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 1 Orlando, Florida, USA December 07-11, 2001
ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English

AB 5-**aza-deoxycytidine** (Decitabine) is a cytosine analogue characterized by modification at the 5 position of Cytosine. In vitro, Decitabine has dual effects on normal and neoplastic cells. At high doses, it appears to cause DNA synthesis arrest due to covalent linkage with DNA-**Methyltransferases** (Mtase), which results in cytotoxicity and apoptosis. At low doses, however, minimal cytotoxicity is observed, and the treated cells exhibit marked reduction in Mtase activity, reduced overall and gene-specific DNA methylation and reactivation of silenced genes, including tumor-suppressor genes. In order to maximize the hypomethylating effects of Decitabine, we have conducted a phase I trial of multiple low dose schedules in patients with relapsed/refractory myeloid malignancies. Initially, patients were treated at 5 mg/m2 IV over 1 hour daily for 10 days (a dose 30 fold lower than the reported MTD). The dose was then escalated to 10, 15 and 20 mg/m2 daily for 10 days. Finally, a group of patients received 15 mg/m2 daily for 15 days then 20 days. A total of 39 patients were enrolled on the study. 3 did not complete the first course (one due to sepsis and death on day 2 and two due to rapidly rising counts) and were excluded from analyses. The drug was well tolerated overall, with one death due to neutropenic sepsis, and 5 asymptomatic elevations in SGPT and/or Bilirubin (four grade 2, one grade 3). Responses were seen at all dose levels, but 15 mg/m2 appeared to induce the most responses, with no further benefit for increasing the dose or duration of administration. There were 7 complete remissions (CR 19.4%, 95% CI 7 to 34%) and 7 partial remissions in the 39 evaluable patients, for a response rate of 39% (95% CI 28 to 61%). Seven additional patients had significant reductions in peripheral and/or bone marrow blasts but did not recover normal hematopoiesis. Responses were seen in refractory/relapsed AML (10/30), MDS (3/4), and CML (2/2). In most patients who responded, there was a very gradual diminution of blasts over 2-4 weeks, and eventual recovery of normal hematopoiesis at 4-5 weeks, suggesting a non-cytotoxic mode of action for this regimen Response

duration ranged from 2 months to 10+ months. DNA methylation studies are ongoing, but p15 demethylation could be observed 5 days after treatment in 2 patients who subsequently achieved remission. We conclude that low-dose Decitabine is an effective agent in myeloid malignancies that appears to induce remissions in part through demethylation rather than cytotoxicity. The recommended (minimal effective) dose of Decitabine for Phase II and combination studies in hematopoietic and solid neoplasms is 15 mg/mg2 IV over 1 hour daily for 10 days.

L58 ANSWER 5 OF 10 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2001027392 MEDLINE
DOCUMENT NUMBER: 20493557 PubMed ID: 10924517
TITLE: Regulation of the promoter activity of interferon regulatory factor-7 gene. Activation by interferon snd silencing by hypermethylation.
AUTHOR: Lu R; Au W C; Yeow W S; Hageman N; Pitha P M
CORPORATE SOURCE: Oncology Center and Department of Molecular Biology and Genetics, The Johns Hopkins University School of Medicine, Baltimore, Maryland 21231, USA.
CONTRACT NUMBER: R01 AI19737-17 (NIAID)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2000 Oct 13) 275 (41) 31805-12.
Journal code: HIV. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF277159
ENTRY MONTH: 200011
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001113

AB The molecular mechanism by which virus induces expression of the early inflammatory genes has not yet been completely elucidated. Previous studies indicated that the virus-mediated transcription of type I interferon (IFN) genes required activation of two members of IFN regulatory factor (IRF) family, IRF-3 and IRF-7, where the expression of IRF-7 was found to be indispensable for the induction of IFNA genes. To determine the factors that regulate expression of IRF-7 gene, as well as its inducibility by type I IFNs, we have isolated and characterized the promoter and first intron of the human IRF-7 gene. This region shows a presence of two potential interferon-sensitive response elements (ISRE/IRF-E). However, only the ISRE present in the first intron was functional and conferred interferon inducibility in a transient transfection assay. Using a pull-down assay with an oligodeoxynucleotide corresponding to this ISRE immobilized to magnetic beads, we have demonstrated that this ISRE binds ISGF3 complex and IRF-1 from the extract of IFN-treated cells but not from the untreated cells. We have further shown that the previously observed lack of expression of IRF-7 in 2fTGH fibrosarcoma cell line, correlated with hypermethylation of the CpG island in the human IRF-7 promoter. The repression of the promoter activity was relieved by treatment with DNA **methyltransferase** inhibitor 5-**aza-deoxycytidine**. In vitro methylation of IRF-7 promoter silenced IRF-7 directed expression of luciferase gene in HeLa cells that express endogenous IRF-7 gene. Whether silencing of IRF-7 by methylation is instrumental for the process of tumorigenesis remains to be determined.

L58 ANSWER 6 OF 10 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 3
ACCESSION NUMBER: 2000:597738 CAPLUS
DOCUMENT NUMBER: 133:264779
TITLE: Aberrant methylation of the Cyclooxygenase 2 CpG

island in colorectal tumors
AUTHOR(S): Toyota, Minoru; Shen, Lanlan; Ohe-Toyota, Mutsumi; Hamilton, Stanley R.; Sinicrope, Frank A.; Issa, Jean-Pierre J.
CORPORATE SOURCE: Johns Hopkins Oncology Center, Baltimore, MD, 21231, USA
SOURCE: Cancer Research (2000), 60(15), 4044-4048
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Cyclooxygenases (COXs) are key enzymes that convert arachidonic acid to prostaglandins. Overexpression of one of the COX isoenzymes, COX2 has been shown to play an important role in colorectal cancer progression. Recently, however, low expression of COX2 has been reported in a subset of colorectal and gastric cancers. Aberrant CpG island methylation and assocd. transcriptional silencing are common in colorectal cancer, and the authors therefore investigated the potential role of methylation in the transcriptional silencing of COX2. The authors examd. the methylation status of the COX2 5' CpG island in a series of tumor cell lines. Among the 33 cell lines examd., dense methylation (>70%) of COX2 was detected in 5 cell lines, and partial methylation was detected in 10 cell lines. Detailed methylation mapping using bisulfite genomic sequencing revealed that loss of expression of COX2 mRNA was closely correlated with methylation of a region upstream of exon 1, and expression could be restored by demethylation using the DNA **methyltransferase** inhibitor 5-**aza-deoxycytidine**. Aberrant methylation of COX2 was also detected in 12 of 92 (13%) unselected sporadic primary colorectal cancers and 7 of 50 (14%) colorectal adenomas. COX2 methylation was strongly assocd. with the presence of the CpG island methylator phenotype, inversely related to p53 gene mutation, and unrelated to microsatellite instability status. The authors propose that COX2 expression in colorectal tumors is modulated by functional factors that favor high expression and by the CpG island methylator phenotype that favors silencing in a subset of cases. These results raise the possibility that tumors with COX2 methylation may be less sensitive to treatment using specific COX2 inhibitors.

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L58 ANSWER 7 OF 10 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 2000184060 MEDLINE
DOCUMENT NUMBER: 20184060 PubMed ID: 10717233
TITLE: GSTP1 CpG island DNA hypermethylation in hepatocellular carcinomas.
AUTHOR: Tchou J C; Lin X; Freije D; Isaacs W B; Brooks J D; Rashid A; De Marzo A M; Kanai Y; Hirohashi S; Nelson W G
CORPORATE SOURCE: The Johns Hopkins Oncology Center and Johns Hopkins University School of Medicine, Baltimore, MD 21287-2411, USA.
CONTRACT NUMBER: CA58236 (NCI)
CA70196 (NCI)
SOURCE: INTERNATIONAL JOURNAL OF ONCOLOGY, (2000 Apr) 16 (4) 663-76.
Journal code: CX5; 9306042. ISSN: 1019-6439.
PUB. COUNTRY: Greece
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200005
ENTRY DATE: Entered STN: 20000518
Last Updated on STN: 20000518

Entered Medline: 20000511

AB Glutathione S-transferases, enzymes that defend cells against damage mediated by oxidant and electrophilic carcinogens, may be critical determinants of cancer pathogenesis. We report here that the pathogenesis of hepatocellular carcinoma (HCC), one of the most common cancers in the world, frequently involves an accumulation of somatic <CpG island> DNA methylation changes at GSTP1, the gene encoding the pi-class glutathione S-transferase. For our study, Hep3B HCC cells and a cohort of 20 HCC tissue specimens were subjected to analysis for GSTP1 expression and for somatic GSTP1 alterations. GSTP1 <CpG island> DNA hypermethylation in HCC DNA was assessed by Southern blot analysis, via a polymerase chain reaction (PCR) assay, and by using a genomic sequencing approach. Hep3B HCC cells failed to express GSTP1 mRNA or GSTP1 polypeptides. Similarly, HCC cells in 19 of 20 HCC cases were devoid of GSTP1 polypeptides. By Southern blot analysis, DNA from Hep3B HCC cells displayed abnormal GSTP1 <CpG island> hypermethylation. Treatment of Hep3B HCC cells in vitro with the DNA **methyltransferase** inhibitor 5-**aza-deoxycytidine** both reversed GSTP1 <CpG island> DNA hypermethylation and restored GSTP1 expression. Using a PCR assay, somatic GSTP1 <CpG island> DNA hypermethylation was also detected in HCC DNA from 17 of 20 HCC cases. Genomic sequencing analyses, undertaken to map 5-methyldeoxycytidine nucleotides located at the GSTP1 transcriptional regulatory region, frequently detected somatic DNA hypermethylation near the gene promoter in HCC DNA. The data indicate that GSTP1 <CpG island> DNA hypermethylation changes appear frequently in human HCC. In addition, the data raise the possibility that somatic GSTP1 inactivation, via <CpG island> hypermethylation, may contribute to the pathogenesis of HCC.

L58 ANSWER 8 OF 10 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 1999361252 MEDLINE
DOCUMENT NUMBER: 99361252 PubMed ID: 10432687
TITLE: Distinct inhibitory effects of 2-chloro-2'-deoxyadenosine and 9-beta-D-arabinosyl-2-fluoroadenine on DNA **methyltransferase** in human T-lymphocytes.
AUTHOR: Wyczechowska D; Ruckemann K; Duley J A; Simmonds A H; Fabianowska-Majewska K
CORPORATE SOURCE: Department of General Chemistry, Medical University of Lodz, Poland.
SOURCE: NUCLEOSIDES AND NUCLEOTIDES, (1999 Apr-May) 18 (4-5) 831-4. Journal code: C5G; 8215930. ISSN: 0732-8311.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199908
ENTRY DATE: Entered STN: 19990910
Last Updated on STN: 19990910
Entered Medline: 19990824

AB The effect of 2-chloro-2'-deoxyadenosine and 9-beta-D-arabinosyl-2-fluoroadenine on DNA **methyltransferase** activity in stimulated human T-lymphocytes was estimated. In comparative studies 5-**aza-deoxycytidine** and deoxyadenosine plus deoxycoformycin were used. These antileukemic compounds demonstrated different effects; both 2CdA and dAdo plus dCF, like 5-aza-dCyt, inhibited the enzyme activity by 85-90% after 72 hours activation of lymphocytes, while the effect of F-ara-A, under the same conditions, was insignificant.

L58 ANSWER 9 OF 10 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:39487 CAPLUS
DOCUMENT NUMBER: 126:139551
TITLE: Reversal of loss of imprinting in tumor cells by 5-aza-2'-deoxycytidine

AUTHOR(S): Barletta, Janet M.; Rainier, Shirley; Feinberg, Andrew P.
CORPORATE SOURCE: Departments Medicine, Johns Hopkins University School Medicine, Baltimore, MD, 21205, USA
SOURCE: Cancer Research (1997), 57(1), 48-50
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB To det. whether loss of imprinting in cancer might be reversed by altering DNA methylation, the authors treated tumor cells with 5-aza-2'-deoxycytidine, a specific inhibitor of cytosine DNA **methyltransferase**. Treated cells showed several significant and reproducible changes. (A) Equal expression of maternal and paternal alleles of insulin-like growth factor 2 switched to predominant expression of a single parental allele. (B) H19 expression was reactivated. (C) Biallelic H19 expression switched to monoallelic expression. (D) Biallelic methylation of H19 switched to preferential allelic methylation. These results imply that abnormally imprinted cells are susceptible to epigenetic modification and that the effect of 5-aza-2'-deoxycytidine on tumor cells with loss of imprinting is not random but specific to one allele.

L58 ANSWER 10 OF 10 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 95254628 MEDLINE
DOCUMENT NUMBER: 95254628 PubMed ID: 7537636
TITLE: Suppression of intestinal neoplasia by DNA hypomethylation.
AUTHOR: Laird P W; Jackson-Grusby L; Fazeli A; Dickinson S L; Jung W E; Li E; Weinberg R A; Jaenisch R
CORPORATE SOURCE: Whitehead Institute for Biomedical Research, Massachusetts Institute of Technology, Cambridge 02142, USA.
CONTRACT NUMBER: F32 CA 09097 (NCI)
R35 CA 44339 (NCI)
SOURCE: CELL, (1995 Apr 21) 81 (2) 197-205.
Journal code: CQ4; 0413066. ISSN: 0092-8674.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199506
ENTRY DATE: Entered STN: 19950615
Last Updated on STN: 19960129
Entered Medline: 19950602

AB We have used a combination of genetics and pharmacology to assess the effects of reduced DNA **methyltransferase** activity on ApcMin-induced intestinal neoplasia in mice. A reduction in the DNA **methyltransferase** activity in Min mice due to heterozygosity of the DNA **methyltransferase** gene, in conjunction with a weekly dose of the DNA **methyltransferase** inhibitor 5-**aza-deoxycytidine**, reduced the average number of intestinal adenomas from 113 in the control mice to only 2 polyps in the treated heterozygotes. Hence, DNA **methyltransferase** activity contributes substantially to tumor development in this mouse model of intestinal neoplasia. Our results argue against an oncogenic effect of DNA hypomethylation. Moreover, they are consistent with a role for DNA **methyltransferase** in the generation of the C to T transitions seen at high frequency in human colorectal tumors.

=> d ibib abs 1-10 l58 kwic

L58 ANSWER 1 OF 10 MEDLINE

ACCESSION NUMBER: 2002211750 IN-PROCESS
DOCUMENT NUMBER: 21942399 PubMed ID: 11948118
TITLE: Silencing of GSTP1 Gene by CpG Island DNA Hypermethylation in HBV-associated Hepatocellular Carcinomas.
AUTHOR: Zhong Sheng; Tang Mandy W; Yeo Winnie; Liu Cuiling; Lo Y M Dennis; Johnson Philip J
CORPORATE SOURCE: Departments of Clinical Oncology [S. Z., M. W. T., W. Y., C. L., P. J. J.] and Chemical Pathology [Y. M. D. L.], Sir Y. K. Pao Centre for Cancer, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, N. T., Hong Kong SAR, China.
SOURCE: CLINICAL CANCER RESEARCH, (2002 Apr) 8 (4) 1087-92. Journal code: 9502500. ISSN: 1078-0432.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20020412
Last Updated on STN: 20020412

AB Purpose and Experimental Design: Glutathione S-transferases, enzymes that defend cells against damage mediated by oxidant and electrophilic carcinogens, may be critical determinants of cancer pathogenesis. In this report, we assess the role of epigenetic silencing of the GSTP1 gene, a gene encoding the pi-class glutathione S-transferase, in the pathogenesis of hepatitis B virus (HBV)-associated hepatocellular carcinomas (HCC). The cell lines Hep3B, HepG2, and a cohort of 43 HBV-associated HCC tissue specimens and corresponding nontumor tissues were subjected to analysis for GSTP1 epigenetic alteration and expression. GSTP1 "CpG" island DNA hypermethylation in the liver cell lines, and the tissue specimens were determined by methylation-specific PCR and correlated with expression of the gene using reverse-transcription PCR, immunoblotting, and immunohistochemistry. RESULTS: GSTP1 CpG island DNA hypermethylation was detected in 28 of 43 (65.1%) HCC tissues and 4 of 40 (10%) corresponding nontumor tissues. GSTP1 protein was absent in those cases showing hypermethylation of the gene. Similarly, DNA from Hep3B and HepG2 cell lines displayed complete GSTP1 hypermethylation in the CpG island, and they failed to express GSTP1 mRNA and the corresponding protein product. Treatment of the cell lines with the DNA **methyltransferase** inhibitor 5-**aza-deoxycytidine** reversed the hypermethylation, and restored GSTP1 mRNA and polypeptide expression. CONCLUSIONS: These data indicate that epigenetic silencing of GSTP1 gene expression by CpG island DNA hypermethylation is common in human HBV-associated HCC. In addition, somatic GSTP1 inactivation via CpG island hypermethylation may contribute to the pathogenesis of this malignancy.

AB . . . and they failed to express GSTP1 mRNA and the corresponding protein product. Treatment of the cell lines with the DNA **methyltransferase** inhibitor 5-**aza-deoxycytidine** reversed the hypermethylation, and restored GSTP1 mRNA and polypeptide expression. CONCLUSIONS: These data indicate that epigenetic silencing of GSTP1 gene. . .

L58 ANSWER 2 OF 10 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 1
ACCESSION NUMBER: 2002:12723 CAPLUS
TITLE: Reversal of GSTP1 CpG island hypermethylation and reactivation of .pi.-class glutathione S-transferase (GSTP1) expression in human prostate cancer cells by treatment with procainamide
AUTHOR(S): Lin, Xiaohui; Asgari, Kekule; Putzi, Mathew J.; Gage, Wesley R.; Yu, Xiang; Cornblatt, Brian S.; Kumar, Arunima; Piantadosi, Steven; DeWeese, Theodore L.; De Marzo, Angelo M.; Nelson, William G.
CORPORATE SOURCE: Department of Oncology, The Johns Hopkins University

School of Medicine, Baltimore, MD, 21231, USA
SOURCE: Cancer Research (2001), 61(24), 8611-8616
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Among the many somatic genome alterations present in cancer cells, changes in DNA methylation may represent reversible "epigenetic" lesions, rather than irreversible "genetic" alterations. Cancer cell DNA is typically characterized by increases in the methylation of CpG dinucleotides clustered into CpG islands, near the transcriptional regulatory regions of crit. genes, and by an overall redn. in CpG dinucleotide methylation. The transcriptional "silencing" of gene expression assocd. with such CpG island DNA hypermethylation presents an attractive therapeutic target: restoration of "silenced" gene expression may be possible via therapeutic reversal of CpG island hypermethylation. 5-Aza-cytidine (5-aza-C) and 5-**aza-deoxycytidine** (5-aza-dC), nucleoside analog inhibitors of DNA **methyltransferases**, have been widely used in attempts to reverse abnormal DNA hypermethylation in cancer cells and restore "silenced" gene expression. However, clin. utility of the nucleoside analog DNA **methyltransferase** inhibitors has been limited somewhat by myelosuppression and other side effects. Many of these side effects are characteristic of nucleoside analogs that are not DNA **methyltransferase** inhibitors, offering the possibility that nonnucleoside analog DNA **methyltransferase** inhibitors might not possess such side effects. Human prostate cancer (PCA) cells characteristically contain hypermethylated CpG island sequences encompassing the transcriptional regulatory region of GSTP1, the gene encoding the .pi.-class glutathione S-transferase (GSTP1), and fail to express GSTP1 as a consequence of transcriptional "silencing.". Inactivation of GSTP1 by CpG island hypermethylation, the most common somatic genome alteration yet reported for human PCAs, occurs early during human prostatic carcinogenesis and results in a loss of GSTP1 "caretaker" function, leaving prostate cells with inadequate defenses against oxidant and electrophile carcinogens. We report here that the drug procainamide, a nonnucleoside inhibitor of DNA **methyltransferases**, reversed GSTP1 CpG island hypermethylation and restored GSTP1 expression in LNCaP human PCA cells propagated in vitro or in vivo as xenograft tumors in athymic nude mice.
REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
AB Among the many somatic genome alterations present in cancer cells, changes in DNA methylation may represent reversible "epigenetic" lesions, rather than irreversible "genetic" alterations. Cancer cell DNA is typically characterized by increases in the methylation of CpG dinucleotides clustered into CpG islands, near the transcriptional regulatory regions of crit. genes, and by an overall redn. in CpG dinucleotide methylation. The transcriptional "silencing" of gene expression assocd. with such CpG island DNA hypermethylation presents an attractive therapeutic target: restoration of "silenced" gene expression may be possible via therapeutic reversal of CpG island hypermethylation. 5-Aza-cytidine (5-aza-C) and 5-**aza-deoxycytidine** (5-aza-dC), nucleoside analog inhibitors of DNA **methyltransferases**, have been widely used in attempts to reverse abnormal DNA hypermethylation in cancer cells and restore "silenced" gene expression. However, clin. utility of the nucleoside analog DNA **methyltransferase** inhibitors has been limited somewhat by myelosuppression and other side effects. Many of these side effects are characteristic of nucleoside analogs that are not DNA **methyltransferase** inhibitors, offering the possibility that nonnucleoside analog DNA **methyltransferase** inhibitors might not possess such side effects. Human prostate cancer (PCA) cells characteristically contain hypermethylated CpG island sequences

encompassing the transcriptional regulatory region of GSTP1, the gene encoding the .pi.-class glutathione S-transferase (GSTP1), and fail to express GSTP1 as a consequence of transcriptional "silencing.". Inactivation of GSTP1 by CpG island hypermethylation, the most common somatic genome alteration yet reported for human PCAs, occurs early during human prostatic carcinogenesis and results in a loss of GSTP1 "caretaker" function, leaving prostate cells with inadequate defenses against oxidant and electrophile carcinogens. We report here that the drug procainamide, a nonnucleoside inhibitor of DNA **methyltransferases**, reversed GSTP1 CpG island hypermethylation and restored GSTP1 expression in LNCaP human PCA cells propagated in vitro or in vivo as xenograft tumors in athymic nude mice.

L58 ANSWER 3 OF 10 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:795150 CAPLUS
DOCUMENT NUMBER: 136:144777
TITLE: 5-Aza-2'-deoxycytidine Induces Histone Hyperacetylation of Mouse Centromeric Heterochromatin by a Mechanism Independent of DNA Demethylation
AUTHOR(S): Takebayashi, Shin-ichiro; Nakao, Mitsuyoshi; Fujita, Naoyuki; Sado, Takashi; Tanaka, Minoru; Taguchi, Hiroshi; Okumura, Katsuzumi
CORPORATE SOURCE: Faculty of Bioresources, Mie University, Tsu, Mie, 514-8507, Japan
SOURCE: Biochemical and Biophysical Research Communications (2001), 288(4), 921-926
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB 5-Aza-2'-deoxycytidine (5-azadC) is widely used as a potent inhibitor of DNA **methyltransferase**. Cells treated with this drug show various phenomena such as the reactivation of repressed genes, change in replication timing, and decondensation of heterochromatin. A no. of studies using this drug have been reported so far but it is still controversial whether such changes are due to 5-azadC-induced demethylation itself or the side effects of the drug. Here we report that 5-azadC treatment induces histone hyperacetylation in mouse centromeric heterochromatin which normally contains methylated DNA and hypoacetylated histones. Treatment also affects the intranuclear distribution of histone deacetylase 2 (HDAC2). However, histone hyperacetylation was not obsd. in DNA **methyltransferase** 1-deficient cells with a reduced level of genomic DNA methylation. Our results suggest that 5-azadC-induced histone hyperacetylation is independent of DNA demethylation and that DNA methylation is not essential for the maintenance of the histone hypoacetylated state in centromeric heterochromatin. (c) 2001 Academic Press.
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
AB 5-Aza-2'-deoxycytidine (5-azadC) is widely used as a potent inhibitor of DNA **methyltransferase**. Cells treated with this drug show various phenomena such as the reactivation of repressed genes, change in replication timing, and decondensation of heterochromatin. A no. of studies using this drug have been reported so far but it is still controversial whether such changes are due to 5-azadC-induced demethylation itself or the side effects of the drug. Here we report that 5-azadC treatment induces histone hyperacetylation in mouse centromeric heterochromatin which normally contains methylated DNA and hypoacetylated histones. Treatment also affects the intranuclear distribution of histone deacetylase 2 (HDAC2). However, histone hyperacetylation was not obsd. in DNA **methyltransferase** 1-deficient cells with a reduced level of genomic DNA methylation. Our results suggest that 5-azadC-induced histone

hyperacetylation is independent of DNA demethylation and that DNA methylation is not essential for the maintenance of the histone hypoacetylated state in centromeric heterochromatin. (c) 2001 Academic Press.

ST **aza deoxycytidine** histone hyperacetylation centromeric heterochromatin DNA demethylation

IT 9037-42-7, DNA **methyltransferase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(5-aza-2'-deoxycytidine induces histone hyperacetylation of mouse centromeric heterochromatin by a mechanism independent of DNA demethylation)

IT 9037-42-7, DNA **methyltransferase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(5-aza-2'-deoxycytidine induces histone hyperacetylation of mouse centromeric heterochromatin by a mechanism independent of DNA demethylation)

L58 ANSWER 4 OF 10 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:209957 BIOSIS
DOCUMENT NUMBER: PREV200200209957
TITLE: Minimal effective dose of the hypomethylating agent Decitabine in hematopoietic malignancies.
AUTHOR(S): Issa, Jean-Pierre (1); Garcia-Manero, Guillermo (1); Mannari, Rajan (1); Thomas, Deborah (1); Giles, Frank (1); Cortes, Jorge (1); Estey, Elihu (1); Kantarjian, Hagop (1)
CORPORATE SOURCE: (1) Department of Leukemia, University of Texas M.D. Anderson Cancer Center, Houston, TX USA
SOURCE: Blood, (November 16, 2001) Vol. 98, No. 11 Part 1, pp. 594a-595a. http://www.bloodjournal.org/. print.
Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 1 Orlando, Florida, USA December 07-11, 2001
ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English

AB 5-**aza-deoxycytidine** (Decitabine) is a cytosine analogue characterized by modification at the 5 position of Cytosine. In vitro, Decitabine has dual effects on normal and neoplastic cells. At high doses, it appears to cause DNA synthesis arrest due to covalent linkage with DNA-**Methyltransferases** (Mtase), which results in cytotoxicity and apoptosis. At low doses, however, minimal cytotoxicity is observed, and the treated cells exhibit marked reduction in Mtase activity, reduced overall and gene-specific DNA methylation and reactivation of silenced genes, including tumor-suppressor genes. In order to maximize the hypomethylating effects of Decitabine, we have conducted a phase I trial of multiple low dose schedules in patients with relapsed/refractory myeloid malignancies. Initially, patients were treated at 5 mg/m2 IV over 1 hour daily for 10 days (a dose 30 fold lower than the reported MTD). The dose was then escalated to 10, 15 and 20 mg/m2 daily for 10 days. Finally, a group of patients received 15 mg/m2 daily for 15 days then 20 days. A total of 39 patients were enrolled on the study. 3 did not complete the first course (one due to sepsis and death on day 2 and two due to rapidly rising counts) and were excluded from analyses. The drug was well tolerated overall, with one death due to neutropenic sepsis, and 5 asymptomatic elevations in SGPT and/or Bilirubin (four grade 2, one grade 3). Responses were seen at all dose levels, but 15 mg/m2 appeared to induce the most responses, with no further benefit for increasing the dose or duration of administration. There were 7 complete remissions (CR 19.4%, 95% CI 7 to 34%) and 7 partial remissions in the 39 evaluable patients, for a response rate of 39% (95% CI 28 to 61%). Seven additional patients had significant reductions in peripheral and/or bone marrow blasts but did not recover normal hematopoiesis. Responses were seen in

refractory/relapsed AML (10/30), MDS (3/4), and CML (2/2). In most patients who responded, there was a very gradual diminution of blasts over 2-4 weeks, and eventual recovery of normal hematopoiesis at 4-5 weeks, suggesting a non-cytotoxic mode of action for this regimen Response duration ranged from 2 months to 10+ months. DNA methylation studies are ongoing, but p15 demethylation could be observed 5 days after treatment in 2 patients who subsequently achieved remission. We conclude that low-dose Decitabine is an effective agent in myeloid malignancies that appears to induce remissions in part through demethylation rather than cytotoxicity. The recommended (minimal effective) dose of Decitabine for Phase II and combination studies in hematopoietic and solid neoplasms is 15 mg/mg2 IV over 1 hour daily for 10 days.

AB 5-**aza-deoxycytidine** (Decitabine) is a cytosine analogue characterized by modification at the 5 position of Cytosine. In vitro, Decitabine has dual effects. . . on normal and neoplastic cells. At high doses, it appears to cause DNA synthesis arrest due to covalent linkage with DNA-**Methyltransferases** (Mtase), which results in cytotoxicity and apoptosis. At low doses, however, minimal cytotoxicity is observed, and the treated cells exhibit. . .

IT . . .
disease; refractory myeloid malignancy: blood and lymphatic disease, drug therapy, immune system disease, mortality, neoplastic disease

IT Chemicals & Biochemicals
5-**aza-deoxycytidine** [Decitabine]: Phase II clinical trial, antineoplastic - drug, hematologic - drug, intravenous administration, pharmacodynamics, phase I clinical trial, toxicity; DNA: methylation; DNA **methyltransferase**; SGPT; bilirubin

RN 2353-33-5 (5-**AZA-DEOXYCYTIDINE**)
2353-33-5 (DECITABINE)
9037-42-7 (DNA **METHYLTRANSFERASE**)
635-65-4 (BILIRUBIN)

L58 ANSWER 5 OF 10 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2001027392 MEDLINE
DOCUMENT NUMBER: 20493557 PubMed ID: 10924517
TITLE: Regulation of the promoter activity of interferon regulatory factor-7 gene. Activation by interferon snd silencing by hypermethylation.
AUTHOR: Lu R; Au W C; Yeow W S; Hageman N; Pitha P M
CORPORATE SOURCE: Oncology Center and Department of Molecular Biology and Genetics, The Johns Hopkins University School of Medicine, Baltimore, Maryland 21231, USA.
CONTRACT NUMBER: R01 AI19737-17 (NIAID)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2000 Oct 13) 275 (41) 31805-12.
Journal code: HIV. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF277159
ENTRY MONTH: 200011
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001113

AB The molecular mechanism by which virus induces expression of the early inflammatory genes has not yet been completely elucidated. Previous studies indicated that the virus-mediated transcription of type I interferon (IFN) genes required activation of two members of IFN regulatory factor (IRF) family, IRF-3 and IRF-7, where the expression of IRF-7 was found to be indispensable for the induction of IFNA genes. To determine the factors that regulate expression of IRF-7 gene, as well as

its inducibility by type I IFNs, we have isolated and characterized the promoter and first intron of the human IRF-7 gene. This region shows a presence of two potential interferon-sensitive response elements (ISRE/IRF-E). However, only the ISRE present in the first intron was functional and conferred interferon inducibility in a transient transfection assay. Using a pull-down assay with an oligodeoxynucleotide corresponding to this ISRE immobilized to magnetic beads, we have demonstrated that this ISRE binds ISGF3 complex and IRF-1 from the extract of IFN-treated cells but not from the untreated cells. We have further shown that the previously observed lack of expression of IRF-7 in 2fTGH fibrosarcoma cell line, correlated with hypermethylation of the CpG island in the human IRF-7 promoter. The repression of the promoter activity was relieved by treatment with DNA **methyltransferase** inhibitor 5-**aza-deoxycytidine**. In vitro methylation of IRF-7 promoter silenced IRF-7 directed expression of luciferase gene in HeLa cells that express endogenous IRF-7 gene. Whether silencing of IRF-7 by methylation is instrumental for the process of tumorigenesis remains to be determined.

AB . . . the CpG island in the human IRF-7 promoter. The repression of the promoter activity was relieved by treatment with DNA **methyltransferase** inhibitor 5-**aza-deoxycytidine** . In vitro methylation of IRF-7 promoter silenced IRF-7 directed expression of luciferase gene in HeLa cells that express endogenous IRF-7. . .

L58 ANSWER 6 OF 10 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 3
ACCESSION NUMBER: 2000:597738 CAPLUS
DOCUMENT NUMBER: 133:264779
TITLE: Aberrant methylation of the Cyclooxygenase 2 CpG island in colorectal tumors
AUTHOR(S): Toyota, Minoru; Shen, Lanlan; Ohe-Toyota, Mutsumi; Hamilton, Stanley R.; Sinicrope, Frank A.; Issa, Jean-Pierre J.
CORPORATE SOURCE: Johns Hopkins Oncology Center, Baltimore, MD, 21231, USA
SOURCE: Cancer Research (2000), 60(15), 4044-4048
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Cyclooxygenases (COXs) are key enzymes that convert arachidonic acid to prostaglandins. Overexpression of one of the COX isoenzymes, COX2 has been shown to play an important role in colorectal cancer progression. Recently, however, low expression of COX2 has been reported in a subset of colorectal and gastric cancers. Aberrant CpG island methylation and assocd. transcriptional silencing are common in colorectal cancer, and the authors therefore investigated the potential role of methylation in the transcriptional silencing of COX2. The authors examd. the methylation status of the COX2 5' CpG island in a series of tumor cell lines. Among the 33 cell lines examd., dense methylation (>70%) of COX2 was detected in 5 cell lines, and partial methylation was detected in 10 cell lines. Detailed methylation mapping using bisulfite genomic sequencing revealed that loss of expression of COX2 mRNA was closely correlated with methylation of a region upstream of exon 1, and expression could be restored by demethylation using the DNA **methyltransferase** inhibitor 5-**aza-deoxycytidine**. Aberrant methylation of COX2 was also detected in 12 of 92 (13%) unselected sporadic primary colorectal cancers and 7 of 50 (14%) colorectal adenomas. COX2 methylation was strongly assocd. with the presence of the CpG island methylator phenotype, inversely related to p53 gene mutation, and unrelated to microsatellite instability status. The authors propose that COX2 expression in colorectal tumors is modulated by functional factors

that favor high expression and by the CpG island methylator phenotype that favors silencing in a subset of cases. These results raise the possibility that tumors with COX2 methylation may be less sensitive to treatment using specific COX2 inhibitors.

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB Cyclooxygenases (COXs) are key enzymes that convert arachidonic acid to prostaglandins. Overexpression of one of the COX isoenzymes, COX2 has been shown to play an important role in colorectal cancer progression. Recently, however, low expression of COX2 has been reported in a subset of colorectal and gastric cancers. Aberrant CpG island methylation and assocd. transcriptional silencing are common in colorectal cancer, and the authors therefore investigated the potential role of methylation in the transcriptional silencing of COX2. The authors examd. the methylation status of the COX2 5' CpG island in a series of tumor cell lines. Among the 33 cell lines examd., dense methylation (>70%) of COX2 was detected in 5 cell lines, and partial methylation was detected in 10 cell lines. Detailed methylation mapping using bisulfite genomic sequencing revealed that loss of expression of COX2 mRNA was closely correlated with methylation of a region upstream of exon 1, and expression could be restored by demethylation using the DNA **methyltransferase** inhibitor 5-**aza-deoxycytidine**. Aberrant methylation of COX2 was also detected in 12 of 92 (13%) unselected sporadic primary colorectal cancers and 7 of 50 (14%) colorectal adenomas. COX2 methylation was strongly assocd. with the presence of the CpG island methylator phenotype, inversely related to p53 gene mutation, and unrelated to microsatellite instability status. The authors propose that COX2 expression in colorectal tumors is modulated by functional factors that favor high expression and by the CpG island methylator phenotype that favors silencing in a subset of cases. These results raise the possibility that tumors with COX2 methylation may be less sensitive to treatment using specific COX2 inhibitors.

L58 ANSWER 7 OF 10 MEDLINE DUPLICATE 4

ACCESSION NUMBER: 2000184060 MEDLINE
DOCUMENT NUMBER: 20184060 PubMed ID: 10717233
TITLE: GSTP1 CpG island DNA hypermethylation in hepatocellular carcinomas.
AUTHOR: Tchou J C; Lin X; Freije D; Isaacs W B; Brooks J D; Rashid A; De Marzo A M; Kanai Y; Hirohashi S; Nelson W G
CORPORATE SOURCE: The Johns Hopkins Oncology Center and Johns Hopkins University School of Medicine, Baltimore, MD 21287-2411, USA.
CONTRACT NUMBER: CA58236 (NCI)
CA70196 (NCI)
SOURCE: INTERNATIONAL JOURNAL OF ONCOLOGY, (2000 Apr) 16 (4) 663-76.
Journal code: CX5; 9306042. ISSN: 1019-6439.
PUB. COUNTRY: Greece
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200005
ENTRY DATE: Entered STN: 20000518
Last Updated on STN: 20000518
Entered Medline: 20000511

AB Glutathione S-transferases, enzymes that defend cells against damage mediated by oxidant and electrophilic carcinogens, may be critical determinants of cancer pathogenesis. We report here that the pathogenesis of hepatocellular carcinoma (HCC), one of the most common cancers in the world, frequently involves an accumulation of somatic <CpG island> DNA methylation changes at GSTP1, the gene encoding the pi-class glutathione

S-transferase. For our study, Hep3B HCC cells and a cohort of 20 HCC tissue specimens were subjected to analysis for GSTP1 expression and for somatic GSTP1 alterations. GSTP1 <CpG island> DNA hypermethylation in HCC DNA was assessed by Southern blot analysis, via a polymerase chain reaction (PCR) assay, and by using a genomic sequencing approach. Hep3B HCC cells failed to express GSTP1 mRNA or GSTP1 polypeptides. Similarly, HCC cells in 19 of 20 HCC cases were devoid of GSTP1 polypeptides. By Southern blot analysis, DNA from Hep3B HCC cells displayed abnormal GSTP1 <CpG island> hypermethylation. Treatment of Hep3B HCC cells in vitro with the DNA **methyltransferase** inhibitor 5-**aza-deoxycytidine** both reversed GSTP1 <CpG island> DNA hypermethylation and restored GSTP1 expression. Using a PCR assay, somatic GSTP1 <CpG island> DNA hypermethylation was also detected in HCC DNA from 17 of 20 HCC cases. Genomic sequencing analyses, undertaken to map 5-methyldeoxycytidine nucleotides located at the GSTP1 transcriptional regulatory region, frequently detected somatic DNA hypermethylation near the gene promoter in HCC DNA. The data indicate that GSTP1 <CpG island> DNA hypermethylation changes appear frequently in human HCC. In addition, the data raise the possibility that somatic GSTP1 inactivation, via <CpG island> hypermethylation, may contribute to the pathogenesis of HCC.

AB . . . from Hep3B HCC cells displayed abnormal GSTP1 <CpG island> hypermethylation. Treatment of Hep3B HCC cells in vitro with the DNA **methyltransferase** inhibitor 5-**aza-deoxycytidine** both reversed GSTP1 <CpG island> DNA hypermethylation and restored GSTP1 expression. Using a PCR assay, somatic GSTP1 <CpG island> DNA. . .

L58 ANSWER 8 OF 10 MEDLINE DUPLICATE 5

ACCESSION NUMBER: 1999361252 MEDLINE
DOCUMENT NUMBER: 99361252 PubMed ID: 10432687
TITLE: Distinct inhibitory effects of 2-chloro-2'-deoxyadenosine and 9-beta-D-arabinosyl-2-fluoroadenine on DNA **methyltransferase** in human T-lymphocytes.
AUTHOR: Wyczechowska D; Ruckemann K; Duley J A; Simmonds A H; Fabianowska-Majewska K
CORPORATE SOURCE: Department of General Chemistry, Medical University of Lodz, Poland.
SOURCE: NUCLEOSIDES AND NUCLEOTIDES, (1999 Apr-May) 18 (4-5) 831-4. Journal code: C5G; 8215930. ISSN: 0732-8311.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199908
ENTRY DATE: Entered STN: 19990910
Last Updated on STN: 19990910
Entered Medline: 19990824

AB The effect of 2-chloro-2'-deoxyadenosine and 9-beta-D-arabinosyl-2-fluoroadenine on DNA **methyltransferase** activity in stimulated human T-lymphocytes was estimated. In comparative studies 5-**aza-deoxycytidine** and deoxyadenosine plus deoxycoformycin were used. These antileukemic compounds demonstrated different effects; both 2CdA and dAdo plus dCF, like 5-aza-dCyt, inhibited the enzyme activity by 85-90% after 72 hours activation of lymphocytes, while the effect of F-ara-A, under the same conditions, was insignificant.

TI Distinct inhibitory effects of 2-chloro-2'-deoxyadenosine and 9-beta-D-arabinosyl-2-fluoroadenine on DNA **methyltransferase** in human T-lymphocytes.

AB The effect of 2-chloro-2'-deoxyadenosine and 9-beta-D-arabinosyl-2-fluoroadenine on DNA **methyltransferase** activity in stimulated human T-lymphocytes was estimated. In comparative studies 5-**aza-deoxycytidine** and deoxyadenosine plus deoxycoformycin were used. These antileukemic compounds demonstrated different effects; both 2CdA and

dAdo plus dCF, like 5-aza-dCyt,. . .
CT Check Tags: Human; Support, Non-U.S. Gov't
*Cladribine: PD, pharmacology
***DNA (Cytosine-5-)-Methyltransferase: AI, antagonists & inhibitors**
*Enzyme Inhibitors: PD, pharmacology
*T-Lymphocytes: DE, drug effects
T-Lymphocytes: EN, enzymology
*Vidarabine: AA, analogs &. . .
CN 0 (Enzyme Inhibitors); EC 2.1.1.37 (DNA (Cytosine-5-)-**Methyltransferase**)

L58 ANSWER 9 OF 10 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:39487 CAPLUS
DOCUMENT NUMBER: 126:139551
TITLE: Reversal of loss of imprinting in tumor cells by 5-aza-2'-deoxycytidine
AUTHOR(S): Barletta, Janet M.; Rainier, Shirley; Feinberg, Andrew P.
CORPORATE SOURCE: Departments Medicine, Johns Hopkins University School Medicine, Baltimore, MD, 21205, USA
SOURCE: Cancer Research (1997), 57(1), 48-50
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To det. whether loss of imprinting in cancer might be reversed by altering DNA methylation, the authors treated tumor cells with 5-aza-2'-deoxycytidine, a specific inhibitor of cytosine DNA **methyltransferase**. Treated cells showed several significant and reproducible changes. (A) Equal expression of maternal and paternal alleles of insulin-like growth factor 2 switched to predominant expression of a single parental allele. (B) H19 expression was reactivated. (C) Biallelic H19 expression switched to monoallelic expression. (D) Biallelic methylation of H19 switched to preferential allelic methylation. These results imply that abnormally imprinted cells are susceptible to epigenetic modification and that the effect of 5-aza-2'-deoxycytidine on tumor cells with loss of imprinting is not random but specific to one allele.
AB To det. whether loss of imprinting in cancer might be reversed by altering DNA methylation, the authors treated tumor cells with 5-aza-2'-deoxycytidine, a specific inhibitor of cytosine DNA **methyltransferase**. Treated cells showed several significant and reproducible changes. (A) Equal expression of maternal and paternal alleles of insulin-like growth factor 2 switched to predominant expression of a single parental allele. (B) H19 expression was reactivated. (C) Biallelic H19 expression switched to monoallelic expression. (D) Biallelic methylation of H19 switched to preferential allelic methylation. These results imply that abnormally imprinted cells are susceptible to epigenetic modification and that the effect of 5-aza-2'-deoxycytidine on tumor cells with loss of imprinting is not random but specific to one allele.
IT Gene, animal
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(H19; reversal of loss of imprinting in tumor cells by **aza-deoxycytidine**)
IT Gene, animal
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(IGF2; reversal of loss of imprinting in tumor cells by **aza-deoxycytidine**)
IT DNA
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(methylation, inhibitors; reversal of loss of imprinting in tumor cells by **aza-deoxycytidine**)

IT Genomic imprinting
Neoplasm
(reversal of loss of imprinting in tumor cells by **aza-deoxycytidine**)

IT Genomic imprinting
Neoplasm
(reversal of loss of imprinting in tumor cells by **aza-deoxycytidine**)

L58 ANSWER 10 OF 10 MEDLINE DUPLICATE 6

ACCESSION NUMBER: 95254628 MEDLINE
DOCUMENT NUMBER: 95254628 PubMed ID: 7537636
TITLE: Suppression of intestinal neoplasia by DNA hypomethylation.
AUTHOR: Laird P W; Jackson-Grusby L; Fazeli A; Dickinson S L; Jung W E; Li E; Weinberg R A; Jaenisch R
CORPORATE SOURCE: Whitehead Institute for Biomedical Research, Massachusetts Institute of Technology, Cambridge 02142, USA.
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AB We have used a combination of genetics and pharmacology to assess the effects of reduced DNA **methyltransferase** activity on ApcMin-induced intestinal neoplasia in mice. A reduction in the DNA **methyltransferase** activity in Min mice due to heterozygosity of the DNA **methyltransferase** gene, in conjunction with a weekly dose of the DNA **methyltransferase** inhibitor 5-**aza-deoxycytidine**, reduced the average number of intestinal adenomas from 113 in the control mice to only 2 polyps in the treated heterozygotes. Hence, DNA **methyltransferase** activity contributes substantially to tumor development in this mouse model of intestinal neoplasia. Our results argue against an oncogenic effect of DNA hypomethylation. Moreover, they are consistent with a role for DNA **methyltransferase** in the generation of the C to T transitions seen at high frequency in human colorectal tumors.

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